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			1646	

DATE MAILED: 09/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/995,225

Applicant(s)

CHEN ET AL.

Examiner

Nirmal S. Basi

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 June 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 29 and 41-61 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 29 and 41-61 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 6/21/06.
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/21/06 has been entered.
2. Amendment filed 6/21/06 has been entered. Claims 29, 41-61 are pending.
3. IDS filed 5/10/05 has been considered.
4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.
5. Claims 29, 41-61 remain rejected under 35 U.S.C. 101 for reasons of record and those given below because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility.
6. Claims 29 and 41-61 are also rejected under 35 U.S.C. 112, first paragraph for reasons of record and those given below. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth in the previous office Action and those below, one skilled in the art clearly would not know how to use the claimed invention.
7. Claims 44-61 remain rejected under 35 U.S.C. 112, first paragraph, for reasons of record and those given below as containing subject matter which was not described in

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the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

8. Applicants request clarification whether the rejection of amended claims 41, 43, and 45 under 35 U.S.C. 112, first paragraph, for failing to comply with the written description requirement has been overcome. The rejection of claims 41 and 43 under written description is withdrawn but the rejection of claim 45 is maintained.

Response to Applicants arguments:

9. Applicants argue:

a) claimed invention has assertion of utility because it can be used in methods of identifying materials which bind to hRUP35, i.e. screening methods.

b) the asserted utility is specific because in this case, the method of identifying materials which bind to a specific receptor, namely (hRUP35), is a method that is not applicable to the general class of receptors or even the subclass of GPCRS. Thus, although Applicants have disclosed a biological function or disease state, such disclosure is not relevant to the question of specific utility.

c) asserted utility is substantial because Applicants have disclosed thalamus-related disorders, specifically, sensorimotor processing and arousal disorders. The present utility is not merely to effect therapeutic control over hRUP35, but rather to treat sensorimotor processing and arousal disorders via that control. The present case clearly links hRUP35, through its expression in the thalamus, to sensorimotor processing disorders and arousal disorders, which were well known to those of skill in the art. It appears to Applicants that the Office's heavy reliance on its position that hRUP35 is not associated with sensorimotor processing and arousal disorders is misplaced and completely lacking in evidentiary support. Consequently, the conclusion that the utility is for treating an unspecified, undisclosed disease or condition is flawed. The facts set forth in the specification or otherwise available to those of skill in the art, and simple logic lead to the conclusion that hRUP35 is associated with sensorimotor processing and arousal disorders, and, thus, a specified, disclosed disease or condition has been associated with hRUP35. Those of skill in the art would readily recognize that hRUP35 is useful for screening candidate compounds for treating diseases or disorders of the thalamus, for example sensorimotor processing disorders and arousal disorders.

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- d) i) hRUP35 is expressed in the thalamus (see Table E);
- ii) proteins located/expressed in the thalamus are associated with sensorimotor processing and arousal
- iii) expression in the thalamus is associated with sensorimotor processing and arousal disorders
- iv) hRUP35 expression results in increased levels of IP3 in thalamus (see Fig. 2)

Therefore, logically, it follows that hRUP35, through its expression in the thalamus, is associated with sensorimotor processing and arousal disorders and, therefore, can be used to screen for compounds to treat such disorders.

e) utility is credible

f) The scientific literature supports Applicants' utility and certainly does not lead one skilled in the art to question it. Those of skill in the art would not doubt Applicants' utility, because earlier literature indicates that GPCRS similarly expressed in the thalamus modulate sensorimotor processing. Those of skill in the art, at least as early as 1994, would have recognized that a GPCR expressed in thalamus can modulate sensorimotor processing and arousal and, furthermore, that a GPCR expressed in thalamus that stimulates IP3 metabolism (for example increases an intracellular level of IP3) can modulate sensorimotor processing and arousal. Applicants argue Salt and Eaton, teach that a GPCR known to stimulate IP3 metabolism modulates sensory response in thalamus, for example response evoked by noxious thermal stimulation of the peripheral receptive field. This teaching is further supported by Miyata et al., Those of skill in the art would note that GPCRS expressed in the thalamus can and do modulate sensorimotor processing and arousal. Thus, those of skill would have less reason to doubt Applicants' assertion that hRUP35, which is expressed in the thalamus, is useful in treating sensorimotor processing and arousal disorder.

Abstract #328 from the February 2006 Keystone Symposium (enclosed) discloses GPR139, which is identical to RUP35. is useful in treating sensorimotor processing and arousal disorders, such as tremor disorder, action tremor disorder, disorders of impaired motor coordination and impaired cognitive performance. The Abstract indicates that GPR139 (RUP35) is associated with motor coordination. In particular, reduction of GPR139 function is associated with impaired motor coordination. Thus, the reference clearly substantiates Applicants' position that hRUP35 is associated with such disorders.

g) While it is true that hRUP35 is a GPCR and, thus, has properties also attributable to other members of the group, the properties of hRUP35 are not based solely on its membership in the GPCR family. hRUP35 increases the level of intracellular IP3, as exemplified in Fig. 2 by transfected 293 cells expressing recombinant hRUP35. Those of skill in the art viewing this data, coupled with the known expression in the thalamus would conclude that hRUP35 increases intracellular IP3 in the thalamus. It is this expression and data, *inter alia*, that lead one skilled in the art to appreciate hRUP35's usefulness in treating sensorimotor processing and arousal disorders.

h) Knowledge of a ligand for hRUP35 is not a requirement for utility. Nor would those of skill in the art doubt an asserted utility merely because the natural ligand is

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unknown, indeed Applicants have previously noted that other well-known receptors (for example the niacin receptor) agonists of which have been identified and used for years without ever deorphanizing the receptor. Those of skill in the art would appreciate Applicants' teachings linking hRUP35 expression to the thalamus and, in turn, to thalamus-related disorders, specifically sensorimotor processing and arousal disorders.

In conclusion applicant is arguing that since hRUP is expressed in the thalamus and it increases IP3 levels in 293 cells it is associated with sensorimotor processing and arousal disorders.

Applicant's arguments have been fully considered but are not found persuasive. Applicants' arguments are flawed on many fronts and filled with ambiguous language that that leads to no solid conclusion.

First, what is the specific disorder or dysfunction that is specifically associated with claimed hRUP. Arguing that hRUP is associated with sensorimotor processing and arousal disorders tells the skilled artisan nothing about the specific disorder. The terms sensorimotor processing and arousal disorders are not defined in the specification. There is no disclosure what disorders are encompassed by the terms sensorimotor processing and arousal disorders .

Examiner has interpreted the words sensorimotor and arouse to mean:

Arouse is to awaken from sleep, to rouse or stimulate to action or to physiological readiness for activity (excite), to awaken from sleep (stir). Sensorimotor means relating to, or functioning in both sensory and motor aspects of bodily activity. Sensor means of or relating to sensation or to the senses, conveying nerve impulses from the sense organs to the nerve centers.

Based on the definitions sensorimotor processing and arousal disorders encompass many different disorders, e.g. inability to sleep, inability to stay awake, inability to keep balance, inability to have an erection, tremors, simple partial epileptic seizure, complex partial seizure, partial with secondary generalized tonic-clonic seizure, absence seizure, myoclonic seizure, tonic-clonic seizure, twitching, Parkinson's disease, inability to move, movement disorders, ataxias, sexual dysfunction etc.. By simply saying hRUP is associated with sensorimotor processing and arousal disorders tells the skilled artisan nothing about the specific disorder that is result of hRUP dysfunction. Will activating the receptor be detrimental or beneficial? Will inhibiting the receptor be detrimental or beneficial? Will the activation of the receptor inhibit a tremor or cause sexual dysfunction? Will the activation of the receptor inhibit a seizure or cause the eye to twitch? Will the activation of the receptor cure Parkinson's disease or cause the person to lose his balance? Further experimentation is required to associate a specific disease or dysfunction with claimed receptor.

The specification discloses " The presence of a receptor in a tissue source, or a diseased tissue, or the presence of the receptor at elevated concentrations in diseased tissue compared to a normal tissue, can be used to correlate location to function and indicate the receptor's physiological role/function and create a treatment regimen, including but not limited to, a disease associated with that function/role." In instant case the presence of the claimed receptor in diseased tissue is not disclosed. The presence of the receptor at elevated concentrations in diseased tissue compared to a normal tissue is not disclosed. The presence of the receptor at elevated concentrations in

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diseased tissue compared to a normal tissue and how it can be used to correlate location to function and indicate the receptor's physiological role/function and create a treatment regimen, including but not limited to, a disease associated with that function/role is not disclosed.

The specification discloses, "the receptors can also be localized to regions of organs. Based on the known or assumed roles/functions of the specific tissues to which the receptor is localized, the putative physiological function of the receptor can be deduced. For example and not limitation, proteins located/expressed in areas of the thalamus are associated with sensorimotor processing and arousal. Proteins expressed in the hippocampus or in Schwann cells are associated with learning and memory, and myelination of peripheral nerves, respectively". The specification discloses claimed receptor is expressed in the thalamus. All applicants' arguments are based on it being expressed in the thalamus. The claimed receptor is also known today as GPR139. Susens et al (Neuropharmacology, Vol. 50, pages 512-520, 2006) (post filing art) discloses GPR139, as message of around 5.5 kb, was exclusively expressed in the brain and was present strongly in E15 and E17 and very weakly in E11 embryos (Fig. 2A). Two human brain-specific northern blots were assayed with a probe covering nucleotides 295–1035 of mouse **GPR139** and showed **predominant expression in putamen, medulla and caudate nucleus. Weaker signals were present in thalamus, amygdala, and spinal cord.** Therefore claimed receptor is not only expressed in the thalamus but also in other areas of the brain suggesting an even broader spectrum of disorders to choose from. It is also important

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to note that Susens detected two GPR39 variants, in addition to the 5.5-kb band a smaller band of around 3.5 kb was present suggesting differential splicing (Fig. 2B). Applicants do not disclose any splice variants. Susens further discloses GPR139 was most prominently expressed in the brain and in E11, E15 and E17 mouse embryos, and a weak signal was present in mouse testis. These results are in agreement with the data obtained by northern-blot analysis and with ESTs, which documented presence of GPR139 in E12.5–E14.5 eyes, E11 spinal cord and adult mouse brain. In the adult mouse brain intense hybridization signals of GPR139 were restricted to the median habenular nucleus (Fig. 3A, B). In situ hybridization analysis on sagittal sections through murine embryos at E12.5 and E18.5 showed that GPR139 transcripts were detected exclusively in distinct regions of the brain and in spinal cord with slightly increasing intensities towards E18.5 (Fig. 4A, B). GPR139 transcripts accumulated in the CA1 area of the hippocampus and over the median habenular nucleus (Fig. 5D, E), and signals of lower intensity were detected over the lateral habenular nucleus (Fig. 5E). In the midbrain area the nucleus oculomotoris (Fig. 6F) and in the hindbrain the nucleus hypoglossis (Fig. 5L) were highlighted by signals. Lower intensities were detected over the piriform and enterorhinal cortices (Fig. 5B, F), the lateral septum (Fig. 5B), the amygdala (Fig. 5C), a few median thalamic nuclei, the reticular nucleus of the thalamus (Fig. 5C, D), the central gray (Fig. 5G), the inferior colliculus (Fig. 5G–I), the medial vestibular nucleus and the inferior olive (Fig. 5I, J). Therefore based on the tissue distribution of GPR139 it is impossible to

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conclusively say what dysfunction specifically results due to claimed receptor dysfunction.

Another potential flaw may be due to interpretation of the data in Figure 2 of the specification. In FIG. 2 of instant application 293 cells were transfected with RUP35 and RUP36 receptor and compared to the control, pCMV. It is concluded that the data indicate that RUP35 receptor is endogenously, constitutively active. RUP35 evidences about a six (6) fold increase in intracellular inositol phosphate (IP3) accumulation when compared to pCMV. Based on this observation applicants conclude that RUP35 increases IP3 in the thalamus. This leap of faith may not be true based on following disclosures:

- a) 293 cells are human embryonic kidney cells (see Han et al, Genomics, 87, pages 552-559, 2006), which have not been shown to be a model for thalamus cells. Han discloses changes in cell culture conditions influence the metabolism of cells, which consequently affects the quality of the products that they produce such as recombinant proteins. Depending on the confluence status of the cells certain genes can be up or down regulated (see page 557, column1). In instant case there is no disclosure of the level of transfection or the amount of recombinant protein produced by the cells disclosed in Figure 2. The increased IP3 levels may be due to over expression and have nothing to do with the natural state of the cells in the thalamus as it pertains to expression and second messenger effects of claimed receptor..
- b) The type of cell and the GPCR expressed is very important to the effect observed. Susens, discloses, stable expression of GPR139 and another related

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GPCR, GPR142, was established in the flip-in cell lines CHO-K1 and HEK-293. In both stable cell lines GPR139 was more strongly expressed than GPR142, as shown for CHO-K1 cells in Fig. 6A–F. In HEK-293 cells GPR139 appeared as monomer and in CHO-K1 cells as dimer (Fig. 6G, middle panel). This indicates that a partner or conditions are present in CHO-K1, but not in HEK-293 cells, which favor dimer formation and potential functions. Susens, discloses, “To analyze possible ligands we concentrated on GPR139 because of its higher protein-expression levels and better presentation at the outer cell membrane.” Susens shows that the effect of certain effectors in brain extract used to stimulate GPR139 is predominantly mediated by an inhibitory G-protein. Susans concludes by suggesting, “The presence of GPR139 in brain areas involved in motor control suggests a function as mediator in locomotor activity. Identification of a ligand or of ligands for both receptors may help to clarify their function.” Therefore even today the function of GPR139 needs to be clarified. The type of cell used will influence the results obtained because it is still not known if the claimed receptor needs to be present as a dimer to function naturally.

c) Gloriam et al (Biochimica et Biophysica Acta, Vol. 1722, pages 235-246, 2005) disclose GPR139 has a very restricted expression pattern and perhaps reflecting that its functional role is more cell-specific and/or that the expression levels are low. Lower expression levels would suggest lower IP3 levels in the brain. This leads to the question does the skilled artisan activate or inhibit hRUP to correct a hRUP specific disorder or dysfunction. What ligands will the skilled artisan use to correct this defect, none are known in the art and none are disclosed in the specification.

Therefore the experimental design and the cells used to analyze the GPCR activity greatly influence the results obtained and therefore cast doubt on the interpretation of the results obtained in 293 cells in Figure 2 of instant application and the conclusion that claimed GPCR increases intracellular levels of IP3 being constitutively active. High levels of IP3 in cells expressing abnormal quantities of hRUP35 does not automatically mean constitutively activation and increased IP3 levels in the thalamus based on the observations above. There is nothing in the specification or prior art that suggests that the claimed isolated hRUP polynucleotide encodes a dysfunctional polypeptide. This means that the skilled artisan still has to do further research to isolate the dysfunctional gene and determine an associated sensorimotor processing and arousal disorder.

Applicants has presented a laundry list of possible diseases that may be associated with dysfunction of claimed GPCR. They may actually have one that actually results from claimed hRUP dysfunction. The question is which one? Defining the disorder by reciting "sensorimotor processing and arousal disorders" provides an unconvincing argument to the office.

The specification discloses diseases and disorders related to receptors located in these tissues or regions include, but are not limited to, cardiac disorders and diseases (e.g. thrombosis, myocardial infarction; atherosclerosis; cardiomyopathies); kidney disease/disorders (e.g., renal failure; renal tubular acidosis; renal glycosuria; nephrogenic diabetes insipidus; cystinuria; polycystic kidney disease); eosinophilia; leukocytosis; leukopenia; ovarian cancer; sexual dysfunction; polycystic ovarian syndrome; pancreatitis and pancreatic cancer; irritable bowel syndrome; colon cancer; Crohn's disease; ulcerative colitis; diverticulitis; Chronic Obstructive Pulmonary Disease (COPD); Cystic Fibrosis; pneumonia; pulmonary hypertension; tuberculosis and lung cancer; Parkinson's disease; movement disorders and ataxias; learning and

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memory disorders; eating disorders (e.g., anorexia; bulimia, etc.); obesity; cancers; thymoma; myasthenia gravis; circulatory disorders; prostate cancer; prostatitis; kidney disease/disorders (e.g., renal failure; renal tubular acidosis; renal glycosuria; nephrogenic diabetes insipidus; cystinuria; polycystic kidney disease); sensorimotor processing and arousal disorders; obsessive-compulsive disorders; testicular cancer; priapism; prostatitis; hernia; endocrine disorders; sexual dysfunction; allergies; depression; psychotic disorders; migraine; reflux; schizophrenia; ulcers; bronchospasm; epilepsy; prostatic hypertrophy; anxiety; rhinitis; angina; and glaucoma. Accordingly, the methods of the present invention may also be useful in the diagnosis and/or treatment of these and other diseases and disorders.

Applicants argue that prior art supports Applicants' utility and certainly does not lead one skilled in the art to question it. Applicants argue Salt and Eaton, teach that a GPCR known to stimulate IP3 metabolism modulates sensory response in thalamus, for example response evoked by noxious thermal stimulation of the peripheral receptive field. The specification does not disclose claimed GPCR stimulated IP3 metabolism modulates sensory response in thalamus, or noxious thermal stimulation of the peripheral receptive field.

Knowing the tissue distribution of a GPCR and its second messenger does not automatically mean that its function is known. Claimed GPCR belongs to the Rhodopsin family of GPCR (see Gloriam et al). This is by far the largest of the five human GPCR families and probably the most diverse based on its ligand specificity. Many members of the Rhodopsin family can be activated by biogenic amines (such as adrenaline, dopamine, histamine and serotonin) and peptides (such as angiotensins, bradykinins, oreostatins, melanocortins, opioids, and galanin). Rhodopsin GPCRs can also be activated by large proteins (such as LH, FSH and TSH), nucleosides and nucleotides (such as adenosine, ATP, UTP and ADP), lipids and eicosanoids (such as

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eukotrienes, prostaglandins, cannabinoids and free fatty acids) and photons. Moreover, the large group of olfactory receptors belong to this family but two thirds of the 900 genes for olfactory receptors are pseudogenes in humans. Only a few members within this subgroup are characterized with regard to ligand specificity and hence the majority of olfactory receptors are orphans. The therapeutic potential of most members in this group has, however, not yet been exploited as many of these receptors are still orphans, without known ligand or physiological function. The showing of a relationship to other GPCRs does not necessarily mean that the biological function or ligand can be determined without extensive experimentation.

Gloriam discloses GPR72 is expressed in regions of the hypothalamus, hippocampus and amygdala in both rodents and humans. GPR72 was previously suggested to be a new NPY receptor but experiments showed that it does not bind NPY-receptor ligands in standard binding assays and this receptor is still an orphan GPCR. Therefore tissue specificity can sometimes be meaningless as it pertains to determining physiological function or dysfunction.

Gloriam discloses that the previously orphan GPCRs, GPR40, GPR41 and GPR43 were found to be low affinity receptors to free fatty acids. These receptors have fairly low similarities to other GPCRs and many of their closest relatives bind peptides, except those that bind leukotrienes (the BLTR receptors). Determining the functionality for claimed invention may even be harder because GPR139 pairs with one previously known orphan receptor and it lacks close relatives.

Lee et al. (Expert Opin. Ther. Targets, Vol 6(2), pages 185-202, 2002) discloses one of the most important tasks of modern pharmacology lies in elucidating the functions of GPCRs. Of particular interest are receptors with recognized expression in the central nervous system. Lee also discloses, "The investigation of the physiological and molecular mechanisms of any signal transduction system requires the identity of both ligand and receptor. For this reason, characterization of oGPCRs remains limited until discovery of their endogenous ligands. Prior to discovery of apelin, the apelin receptor was known to be expressed in the CNS and in the periphery, being especially abundant in developing cardiovascular systems with an additional role as a HIV coreceptor in vitro. However, the physiological roles of the receptor were still undetermined for many years. With the identification of the apelin peptide, there is now evidence of several physiological functions, including the modulation of blood pressure, drinking behavior and immune system function" Lee also discloses many examples where the GPCR and its associated G protein are known, therefore the second messenger is also known but extensive experimentation still is required to discover a physiological function. Lee further highlights the problem of assigning function based on tissue specificity by the example on page 194. Lee discloses there remain several somatostatin-like (and closely-related opioid-like) oGPCR, which have yet to be paired with an endogenous ligand. The genes encoding the oGPCRs named GPR7 and GPR8 were both discovered in 1995, shown to be expressed in rat brain in 1999 (GPR7 and GPR8 are both expressed in discrete regions of the brain and GPR8 appears to be species specific, i.e. absent in rodents) did not bind opioid receptor sub-type-specific

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compounds or somatostatin. The Lee article was published in 2002, seven years after the discovery of GPR7 and GPR8. Another oGPCR, SALPR, expressed in the brain, particularly in the substantia nigra and pituitary, with some expression in the periphery awaits the identification of its specific endogenous ligand. Therefore determining the physiological function of a GPCR and its endogenous ligand is no easy task, even knowing its tissue specificity.

Applicant present Abstract #328 from the February 2006 Keystone Symposium (enclosed) which discloses GPR139 knock out mice showed impairment of motor function as evaluated by using runway and open field gait analyses, retard, balance beam, and other tests. At two months of age mice showed no impairment in any of these behaviors. At five months of age the mice showed impairment in balance. The conclusion was GPR139 null mutants appear to have a primary age-related balance deficit. Based on this post filing abstract (2006) applicant argues their invention is useful in treating sensorimotor processing and arousal disorders, such as tremor disorder, action tremor disorder, disorders of impaired motor coordination and impaired cognitive performance. Applicants further state, "Thus, the reference clearly substantiates Applicants' position that hRUP35 is associated with such disorders." The results disclosed in Abstract #328 were neither disclosed by applicant or could have been predicted from applicants' disclosure. How does applicants observation that hRUP35 expression in thalamus and increased IP3 levels in 293 cells lead to the prediction that mice lacking hRUP35 would have a balance deficit at five months? Applicants had no way of predicting the function based on the lack of the expression of

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hRUP35 gene at the time of filing instant application. Further the lack of the polynucleotide in humans has not been determined. A disease state having a dysfunction in hRUP35 that results in a balance disorder in humans has not been shown. Therefore applicant cannot use post-filing art to assert utility on their claimed invention.

Examiner is not disputing that the claimed invention encodes a GPCR but that said GPCR does not have a specific, substantial and credible utility. Although the claimed receptor has been shown to be expressed in the thalamus there is no disclosure of the specific association with a sensorimotor processing or arousal disorder. The determination of the specific association with a sensorimotor processing or arousal disorder requires further research. Unlike the argued agonists of the niacin receptor no agonists or antagonists of RUP35 are disclosed which can be used to support a specific, substantial and credible utility. Again the determination of said ligands and their specific use requires further research. Unlike the niacin receptor agonist, which can be used to raise HDL levels in man, no agonists or antagonists are disclosed for RUP35 which have a specific use such as raising HDL levels. When the claimed GPCR is compared to Example 12 of Revised Interim Utility Guidelines Training Materials said GPCR has no specific disclosed function or specific ligands that can be used to support utility. Since neither the specification nor the art of record disclose any activities or properties that would constitute a real world context of use for the claimed hRUP35 further experimentation is necessary to attribute a utility to the claimed hRUP35. The instant application does not disclose the biological role of hRUP35 or its

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significance. The utilities are not considered to be specific and substantial because the specification fails to disclose any particular function or biological significance for the hRUP35 of the instant invention. The disclosed protein, whose cDNA has been isolated, is said to have a potential function based upon its amino acid sequence similarity to other known proteins. After further research, a specific and substantial credible utility might be found for the claimed isolated compositions. This further characterization, however, is part of the act of invention and until it has been undertaken, applicants claimed invention is incomplete.

Therefore claims 29, 41-61 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility.

A specific utility is a utility that is specific to the subject matter claimed, as opposed to a general utility that would be applicable to the broad class of the invention. A "substantial utility" is a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. A "well established utility" is a utility that is well known, immediately apparent, or implied by the specifications disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art. A well-established utility must also be specific and substantial as well as credible.

Based on the record, there is not a "well established utility" for the claimed invention. Applicant has asserted utilities for the specifically claimed invention of claims 29, 41-61.

Applicant has classified the GPCR of SEQ ID NO:15 encoding the polypeptide of SEQ ID NO:16 into the superfamily of GPCRs. The specification discloses the GPCR of SEQ ID NO:16 can be used to identify test compounds which bind said receptor and treat diseases associated with hRUP35 dysfunction. The GPCR of SEQ ID NO:16 is disclosed is to be involved in a variety of unrelated disease states. It noted that neither the **specific** activity of GPCR of SEQ ID NO:16 or the **specific** treatable disease associated with the GPCR of SEQ ID NO:16 is disclosed. Ligands that bind or activate said GPCR are not disclosed. In light of the specification the skilled artisan cannot come to any conclusions as to the function of the hRUP35 polypeptide or its encoding polynucleotide. The utility of claimed hRUP35 cannot be implicated solely from homology to the proteins known in the art or from its expression pattern because the art does not provide teaching stating that all GPCRs found in the thalamus have the same activity, same effects, the same ligands and are involved in the same disease states. In light of the specification and art the skilled artisan cannot come to any conclusions as to the function of claimed polynucleotide or its encoded protein. There is no disclosure provided within the instant specification on what specific function the protein of SEQ ID NO:16 possesses, or how to use compounds that bind said protein. No disease states are disclosed that are directly related to hRUP35 polypeptide dysfunction.

The specification fails to disclose, what specific disease is associated with claimed receptor dysfunction or what drugs affect a specific claimed receptor function. The GPCR may have utility in the future, when it has been further characterized (e.g. its

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dysfunction or function correlated with a disease state) and its ligand characterized. The inclusion in the family of G protein coupled receptors (GPCR) does not constitute either a specific and substantial asserted utility or a well-established utility for that particular GPCR or protein. This is analogous to all proteins or GPCRs can be used as protein markers on a gel.

Specification discloses claimed receptors are useful in screening but the specification does not disclose what claimed receptor specifically regulates and what specific disease the receptor is a target for. What would be the use of using the claimed receptor on a panel for drug screening? The receptor has no known ligand or known function. How would one use the compounds that interacted with said orphan receptors? The specification provides a diverse list of disease states that may be involved in receptor dysfunction. It is unpredictable what ligands will bind to orphan receptors, and further the functional effects of ligand binding may remain uncertain even after extensive experimentation. What is the utility for a ligand, in many cases with no known function, that binds to a receptor of no known function? The ordinary artisan can only speculate on the utility for the ligand and receptor. A utility to orphan receptor cannot be assigned without knowledge of what disease is associated with claimed receptor dysfunction or what drugs/ligands affect a specific claimed receptor function. Members of a sub-family of G-protein-coupled receptors are also highly divergent in their effects, as highlighted by Murdoch et al (Blood, Volume 95, No.10, pages 3032-3043, 2000), in the discussion of cytokine G-protein-coupled receptors. The utility of claimed receptor cannot be implicated solely from homology to known G-protein

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coupled receptors or their protein domains because the art does not provide teaching stating that all members of family of G-protein coupled receptors must have the same effects, the same ligands and be involved in the same disease states, the art discloses evidence to the contrary. The specification has not even used protein domains/homology to predict the activity of the protein. Murdoch discloses the superfamily of G-protein-coupled receptors are highly divergent in their effects and include receptors for hormones, neurotransmitters, paracrine substances, inflammatory mediators, certain proteinases, taste and odorant molecules, and even photons and calcium ions. Further, the G-protein that interacts with the claimed orphan receptor and is required for the signal transduction activity is unknown. Watson (The G-Protein Linked receptor Facts Book, pages 2-6 and 223-230, 1994) states **"it has therefore not been possible to identify consensus amino acid sequences that confer G-protein specificity, and thus G-protein interactions cannot be predicted from the primary amino acid sequence"**. Therefore the disclosure of Watson predicts, using the primary structure of the G-protein coupled receptor the skilled artisan cannot predict its associated G-protein or its ligand. G-protein coupled receptors are highly specialized and ligand specific proteins. The superfamily of seven transmembrane domain G-protein coupled receptors are specialized proteins designed for chemical recognition of ligands and subsequent transduction of information encoded in those ligands to the machinery of the cell, and the G-protein coupled receptors interact with alkaloids, biogenic amines, peptides, glycoprotein hormones, light and odorants (Terry Kenakin, Pharmacological Reviews, Vol. 48, No.3, pages 413-462), see page 413. Kenakin also

states, "To achieve information transfer, the ability to bind ligands to a recognition domain and allosterically transmit the presence of that ligand to an intracellular domain appears to be a specialized feature of 7TM receptors. The very properties that define receptors as such also impart unique protein behaviors to receptors, and these behaviors, in turn, affect drug activity", page 414, column 1, second paragraph. Bork (Nature Genetics, Vol. 18, pages 313-318, 1998) provide a review article disclosing the problems of using homology detection methods to assigning function to related members of a family. Bork discloses: a) "While current homology detection methods can cope with data flow, the identification, verification and annotation of functional features need to be drastically improved", page 313, column 1, Abstract, b) there are two bottle necks that need to be overcome en route to efficient functional predictions from protein sequences, i.e., "First, there is the lack of a widely accepted, robust and continuously updated suite of sequence analysis methods integrated into coherent and efficient prediction system. Second, there is considerable 'noise' in the presentation of experimental information, leading to insufficient or erroneous function assignment in sequence databases", page 313, column 1, third paragraph, c) **"In-depth analysis of protein sequences often results in functional predictions not attained in the original studies"**, page 313, column 2, last paragraph, d) **"However, more often than not, it is clear that the cellular role of the protein in question differs from that of the detected homologue(s) and there is currently no automatic means to establish how much functional information can be legitimately transferred by analogy from homologue to the query"**, page 315, column 2, last paragraph, e)

pertaining to predictions of protein function, "Do not simply transfer functional information from the best hit. The best hit is frequently hypothetical or poorly annotated; other hits with similar or even lower scores may be more informative; even the best hit may have a different function", while "many proteins are multi functional; assignment of a single function, which is still common in genome projects, results in loss of information and outright errors" and "It is typical that the general function of a protein can be identified easily but the prediction of substrate specificity is unwarranted; for example, many permeases of different specificity show approximately the same level of similarity to each other", page 316. Karp (Bioinformatics, Vol. 14, No.9, pages 753-754, 1998) has disclosed the problems of using functional prediction based on homology analysis. Karp states, a) "Although we know the accuracy with which sequence homologs can be determined, we know little about the accuracy of the overall process of assigning function by homology, page 753, column 2, second paragraph, b) "We have more faith in the correctness of those sequences whose functions we determined experimentally, rather than through computational means, page 753, column 2, last paragraph, c) "research is required to estimate the error rate of functional annotation by different methods of computational sequence analysis", page 754, column 2, last paragraph. Bork (Current Opinion in Structural Biology, Vol. 8, pages 331-332, 1998), discusses the problems with deriving biological knowledge from genomic sequences and states, "structural similarity does not lead to iron-clad functional predictions" page 331, column 2 last paragraph, "Structural similarity does not necessarily mean a common evolutionary origin" page 332, column 1, second paragraph, and **"Today, what we**

predict from sequences is at best fragmentary and qualitative", page 332, column 2, second paragraph.

Based on the art, the limited homology of claimed GPCR to other proteins cannot be used to predict its function. The following articles are also cited as evidence for the unpredictability of determining a function or ligand of claimed invention based on homology of GPCRs. Further there is the even greater unpredictability of using the claimed invention to treat a disease related to hRUP35 dysfunction.

Civelli et al (Civelli et al, Pharmacology and Therapeutics, November 8, pages 1-8, 2005) discloses that all 7 transmembrane receptors are not GPCRs (page 2, column 1). GPCRs are activated by a plethora of transmitters and have a broad spectrum of interactions. **The role of GPCRs in various tissues may be different although the second messengers that result from its initial activation are probably the same.** Most GPCRs started as orphan receptors and the discovery of new members found by homology screening suffers from one obvious problem, the receptors found lack their pharmacological identities, their natural ligands (page 2). **The pursuit to unravel their identities has led to fishing expeditions. The number of orphan GPCRs has steadily increased and at this time the GPCRs outnumber the known potential ligands.** Researchers utilize orphan receptors as baits to isolate their natural ligands, which is meant to identify novel transmitters (page 3). Civelli also discloses the discovery of the natural ligand is no easy task, and specifically states, "GPCRs have been depolarized at a rate of 7-8 per year from 1999 until 2004. This was mostly the result of large-scale random screening of practically all molecules known to exist in cell",

(page 4, column 2). There is no rule for predicting the affinity constant of a natural ligand at a particular receptor. The level of receptor expression in a transfected cell can affect ligand potency and is subject to artifacts. Belonging to a family of GPCRs does not insure that all members will bind the same ligand or have the same effects. The recently discovered Mas-related GPCRs, orphan receptors, bind a variety of structurally diverse transmitters (ligands), Rfamide peptides for some mouse Mrgs and cortistatin for two human Mrgs, adenine for rat Mrg and beta-alanine for an Mrg found in human, rat and mouse (column 2, page 5). The matched transmitters are specific to particular Mrgs and activate them efficiently. By the mid-1990s approximately 90 transmitters were known, since then, a dozen new transmitters have been found and it is expected that the remaining 120 orphan GPCRs will lead to the discovery of at least 50 more transmitters (page 6, column 1). **There is no doubt that orphan GPCRs are used as potential drug targets but there is no marketed drug directed at any of the ones that have been depolarized since 1995 (page 6, column 1). Many targets even when recognized of therapeutic interest have showed no value for drug screening (table 2).**

Hancock (Hancock, A.A., Biochemical Pharmacology, Vol. 71, pages 1103-1113, 2006) discloses although histamine H3 receptor (GPCR) was identified pharmacologically in 1993, and despite widespread pharmaceutical interest in the target, no compound interacting specifically with this site has undergone successful clinical examination to develop the necessary proof-of-concept data. The pharmacological effects of known H3 ligands are complex and diverse, since these

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agents may act both as agonists and antagonists in different systems. Moreover, other compounds show inverse agonism in some models but neutral antagonistic activity in others (see abstract).

Feng et al (Feng et al., *Kidney Research*, May, Vol. 67, Issue 5, pages 1731-1738, 2005) discloses the heterogeneity for a GPCR AT2 receptor in both ligand binding and induction of arachidonic acid release. The AT2 receptor exhibits distinct biochemical and biological properties compared to its highly homologous orthologues (91% homologous in overall amino acid sequence) of rat, mouse and human. The reducing agent DTT inactivates the rabbit orthologue but potentiates the others in ligand binding. Rabbit AT2 receptor but not the other orthologues, induces arachidonic acid release in various cell systems when stimulated with Ang II and CGP42112A, the peptide antagonist. Mutagenesis studies and sequence analysis further indicate that residues His106, Asp188 and Thr393 are responsible for DTT inactivation and residues Val209 and Val249 are partially responsible for arachidonic acid release (see Abstract)

Marchese et al (Marchese et al., *TIPS*, Vol. 20, pages 370-375, September 1999) discloses the search for novel GPCR genes (cloning by low stringency hybridization to cDNA/genomic DNA libraries) has far outpaced the identification of novel endogenous ligands, more than 80 orphan GPCRs are awaiting a ligand. Many orphan GPCRs are found to be similar to known GPCRs. Where the identity reaches the threshold of approximately 45% it is likely that the receptors will share a common ligand but **this rule is not without exception** (page 371, column 1)). For example the orphanin RQ/nociceptin receptor (has approximately 65% amino acid identity to opioid

receptors but does not have high affinity for opioid peptides). **Many GPCR subtypes have less than 40% amino acid identity, in which case sequence comparison might not be profitable.** Moreover because the ligand-binding pocket has not been described fully for any receptor, it is not feasible to predict ligand identity. There are no signature amino acids that predict either the nature of the ligand or the identity of the interacting Galpha subunit type(s) (page 371). **Further, the elusive nature of certain labile natural agonists could be a significant hindrance to the discovery of orphan ligands, as there is no reason to believe that the remaining orphan GPCR ligands will all prove to be peptides.** Recently, new complexities have added to the general approach to studying orphan GPCRs. The efficient binding of a ligand to the receptor may require the co-expression of a co-factor protein, e.g. receptor activity modifying protein 1 (RAMP1) in case of amylin binding to orphan GPCR calcitonin receptor-like receptor. Heterodimerization of two subunits may be required for formation of a functional receptor, e.g. GABAb receptor (page 374). The characterization of some GPCR might be more complex than expected, perhaps indicating that functional assays should begin to include co-expression of related orphan GPCRs.

Vanti (Vanti et al., Biochemical and Biophysical Research Communications, Vol. 35, pages 67-71, 2003) discloses the **sequence of a receptor does not necessarily provide insights into the nature of its cognate ligand and therefore such receptors are termed orphan GPCRs.** Vanti, further discloses while some GPCRs, e.g. GPR133 and GPR134, may be nearly identical (95%) they are expressed in different CNS tissues suggesting that this family of receptors may have diverse roles in

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the CNS (page 70, column 1). Further Vanti discloses the efforts to identify and catalog all human GPCR-encoding genes are ongoing, and these efforts have resulted in the identification of entirely novel signaling systems such as apelin, melanin-concentrating hormone, metastin and urotensin (page 70, column). Based on Vanti's observation it is highly possible that the claimed GPCR may signal through a novel signaling system. The claimed receptor, based on the preceding references could also have a novel natural ligand that as of yet, has not been identified or purified.

Mutations in a receptor can affect function. Vanti et al (Vanti et al., Genomics 82, 531-536, 2003) discloses that null mutations can arise in a GPCR that renders it truncated and non-functional). Therefore, in the case of the Vanti variant the wrong probe would not detect anything. The GPCR may also be present in other tissues than indicated. The method used of detection is very important. For example, Ta-Tung (Ta-Tung et al, Gene, Vol. 278, pages 41-45, 2001) discloses the assay and tissue used is very important in determining the information gleaned. Ta-Tung discloses (page 49, column 2) that although PSGR (a GPCR) RNA could not be detected by northern analysis in total RNA from whole brain tissue, RT-PCR analysis of five human brain tissue analyses of five regions did reveal the presence of PSGR mRNA specifically in the olfactory epithelium and medulla oblongata (Fig. 3). Based on the wide spread distribution of claimed polynucleotide there is insufficient information provided on which to base a utility of using hRUP35 as a marker for a disease state.

Further, the ability of a GPCR to increase second messenger levels of a compound (e.g. calcium, IP3) by interaction with a G protein in a specific cell type does

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not mean all GPCRs will have the same physiological function. Even if a GPCR (with known function) increases second messenger levels, for example IP3 levels, in a specific cell, the art discloses that another receptor, which also affects IP3 levels, may have a completely different biological function. Cells are exposed to many extracellular stimuli, yet they respond appropriately only to specific signals, often by means of just a handful of intracellular messengers. There is more to specificity than the controlled expression of signaling proteins. Taylor (Taylor et. al., Calcium signaling:IP3 rises... and again, Current Biology, Vol. 11:R352-R353, 2001), discusses these issues at length and state," **Even within a single cell, different receptors may use the same intracellular messenger molecule to very different effect**", page R352. The ability of GPCRs to interact with other proteins in the cell and the effect of feedback mechanisms allow them to use the same proteins, e.g. Gq proteins in the case of IP3, or second messenger pathways but have very different effects. For example, Taylor (page R352, column 2) discloses that in pancreatic acinar cells cholecystokinin and acetylcholine receptors use the same Gq proteins to stimulate phospholipase C and so trigger Ca²⁺ release from intracellular stores, yet the patterns of Ca²⁺ signals they evoke are quite different". Such diversity sits uneasily with mechanisms wholly dependent on Ca²⁺ regulation of IP3 receptors. The diversity of signal transduction also applies to receptor subtypes. For example, stimulation of one subtype of metabotropic glutamate receptor, mGluR5, evokes Ca²⁺ spikes via IP3, but stimulation of another subtype expressed in the same cell, mGluR1 depends upon a single Ca²⁺ transient. The difference depends upon a single PKC phosphorylation site in mGluR5 (see Taylor, page R354, column 1).

The versatility of the signaling mechanism in cells is also discussed by Berridge et al (Berridge et al, The versatility and universality of calcium signaling, Nature Reviews Molecular Cell Biology, Vol. Pages 11-21, 2000). Berridge discloses the versatility of the signaling mechanism is enhanced by having different second messenger mobilizing molecules linked to separate input signals. Therefore in a given cell two separate molecules linked to the same second messenger such as IP3 can have different effects on the cell.

Therefore, references discussed above disclose the unpredictability of assigning a function to a particular protein based on homology, especially one that belongs to the family of GPCRs, which have very different ligand specificity and functions. The discovery of the endogenous ligands will help determine the precise physiological role for each orphan GPCR. As the functions of these novel receptors are uncovered, they could become targets for the development of new pharmacological therapies for diseases not previously considered amenable to pharmacological therapy, but this requires further research and therefore the invention is not complete.

It can be argued the GPCR of SEQ ID NO:16 is useful tool as a reagent or a molecular target in the diagnosis and treatment of GPCR mediated disorders. All members of the GPCR protein family have a utility in selectively screening of candidate drugs that target GPCRs. However, for a utility to be well established it must be specific, substantial and credible. In this case, as all receptors are in some combination useful in selectively screening of candidate drugs that target GPCRs and in toxicology testing. However, the particulars of screening of candidate drugs, that target GPCR of

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SEQ ID NO:16, and in toxicology testing are not disclosed in the instant specification. Neither the candidate drugs or toxic substances nor the susceptible organ systems are identified. Therefore, this is a utility, which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA, but is only potential with respect to GPCR of SEQ ID NO:16. Because of this, such a utility is not specific and does not constitute a well-established utility. Further, because any potential diagnostic utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in practical form. Moreover, use of the claimed polynucleotide encoding hRUP35 for screening compounds that are a target for GPCR of SEQ ID NO:16 is only useful in the sense that the information that is gained from the assay and is dependent on the effect it has on the protein, and says nothing with regard to each individual member of the GPCR family. Again, this is a utility, which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA. Even if the expression of Applicants individual GPCR is affected by a test compound in an assay for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the individually claimed method of using claimed GPCR has no well-established use. The artisan is required to perform further experimentation on the claimed GPCR itself in order to determine to what use any information regarding this protein could be put.

With regard to diagnosis of disease, in order for a protein/polynucleotide to be useful, as asserted, for diagnosis of a disease, there must be a well established or

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disclosed correlation or relationship between the GPCR of SEQ ID NO:16 and a disease or disorder. The presence of GPCR of SEQ ID NO:16 encoded by the polynucleotide of SEQID NO:15 in tissue is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed GPCR and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the GPCR of SEQ ID NO:16 to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the GPCR of SEQ ID NO:16 is either present only in, e.g. cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. over expression). Evidence of a differential expression might serve as a basis for use of hRUP35 as a diagnostic for a disease. However, in the absence of any disclosed relationship between the hRUP35 and any disease or disorder and the lack of any correlation between the claimed GPCR with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. Congress intended that no patent be granted on a chemical compound whose sole utility consists of its potential role as an object of use testing. *Brenner*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. 101.

Further, hRUP35 belongs is a family in which the members have divergent functions based on which tissues the protein is expressed or administered to. Assignment to this family does not support an inference of utility because the members are not known to share a common utility. There are some protein families for which assignment of a new protein in that family would convey a specific, substantial and credible utility to that protein. For example, some families of enzymes such as proteases, ligases, telomerases, etc. share activities due to the particular specific biochemical characteristics of the members of the protein family such as non-specific substrate requirements, that are reasonably imputed to isolated compositions of any member of the family. The diversity of the GPCRs has already been described. Without some common biological activity for the family members, a new member would not have a specific or substantial utility when relying only on the fact that it has structural similarity to the other family members. The members of the family have different biological activities, which may be related to tissue distribution, but there is no evidence that the claimed compounds share any one of diverse number of activities. That is, no activity is known to be common to all members. To argue that all the members can be used for drug screening, toxicology testing and diagnosis, is to argue a general, nonspecific utility that would apply to virtually every member of the family, contrary to the evidence. Further, any compound could be considered as a regulator or modulator of tissue in that any compound, if administered in the proper amount, will stimulate or inhibit tissue. For example, salt, ethanol, and water are all compounds which will kill cells if administered in a great enough amount, and which would stimulate

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cells from which these compounds had been withheld, therefore, they could be considered regulators or modulators of tissue. However, use of these compounds for the modulation of tissue would not be considered a specific and substantial utility unless there was some disclosure of, for example, a specific and particular combination of compound/composition and application of such in some particular environment of use.

Without knowing a biological significance of the claimed GPCR, one of ordinary skill in the art would not know how to use the claimed invention in its currently available form in a credible real world manner based on the diversity of biological activities possessed by the GPCR family. Contrast *Brenner*, 148 USPQ at 694 (despite similarity with adjacent homologue, there was insufficient likelihood that the steroid would have similar tumor-inhibiting characteristics), with *In re Folkers*, 145 USPQ 390, 393 (CCPA 1965) (some uses can be immediately inferred from a recital of certain properties) or *In re Brana*, 34 USPQ 1436, 1441 (Fed. Cir. 1995) (evidence of success in structurally similar compounds is relevant in determining whether one skilled in the art would believe an asserted utility; here, an implicit assertion of a tumor target was sufficiently specific to satisfy the threshold utility requirement).

The assertion that the claimed invention has utility in drug screening, drug development and disease diagnosis, do not meet the standards for a specific, substantial or well-established utility for reasons set forth above. None of the utilities identified have been demonstrated to be specific to the polypeptide of SEQ ID NO:26. One of ordinary skill in the art must understand how to achieve an immediate and practical benefit from the claimed species based on the knowledge of the class.

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However, no practical benefit has been shown for the use of the hRUP35. Applicant has failed with respect to hRUP35, has not described the family of GPCRs in enough detail to show, by a preponderance of the evidence, that hRUP35 has any substantial use. The record shows that the family of proteins having GPCR domains is diverse, and has such a broad definition, that a common utility cannot be defined. Moreover, the evidence of record is inadequate to determine the disease(s), drug(s) or toxicological screen(s) for which the compounds would be useful. In *Brenner*, the Court approved a rejection for failure to disclose any utility for a compound where the compound was undergoing screening for possible tumor-inhibiting effects and an adjacent homologue of the compound had proven effective. *Brenner*, 148 USPQ at 690. Here, there is no evidence that the claimed isolated compounds have any utility.

For all the above reasons, the disclosure is insufficient to teach one of skill in the art how to use the invention.

The use of the claimed invention for screening assays, drug discovery, and disease diagnosis are not substantial utilities. The question at issue is whether or not the broad general assertion that hRUP35 might be used for some diagnostic application in the absence of a disclosure of which diagnostic application would be considered to be an assertion of a specific, substantial, and credible utility. For reasons set forth above the disclosure satisfies none of the three criteria. See *In re Kirk*, 153 USPQ 48, 53 (CCPA 1967) (quoting the Board of Patent Appeals, We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the

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requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates.)

The prior rejection under 101 followed *Brenner v. Manson*. In that case, the absence of a demonstrated specific utility for the claimed steroid compound was not ameliorated by the existence of a demonstrated general utility for the class. Unlike *Fujikawa v. Wattanasin*, where there were pharmaceutically acceptable in vitro results, here, there is nothing other than relatively low levels of sequence homology to a broad and diverse family of proteins having distinct modes of activity, and no disclosed common mode of action. A rejection under 112, first paragraph, may be affirmed on the same basis as a lack of utility rejection under 101. See, e.g., *In re Swartz*, 56 USPQ2d 1703 (Fed. Cir. 2000); *In re Kirk*, 153 USPQ 48 (CCPA 1967). Further since the claimed hRUP35 has no utility, vectors hRUP35 polynucleotide, cell comprising said vector, and methods of its use hRUP35 polynucleotide or its constructs are also rejected for lack of utility.

10. Claims 29 and 41-61 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Since

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neither the specification nor the art of record disclose any activities or properties that would constitute a real world context of use for the claimed cDNA encoding hRUP35 further experimentation is necessary to attribute a utility to the claimed polynucleotides and fragments thereof.

Further claims 44-61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 44-45 and 57-61 are drawn to an isolated polynucleotide, wherein said polynucleotide comprises a nucleic acid sequence encoding an endogenous human G protein-coupled receptor, said nucleic acid sequence being obtainable by a process comprising performing polymerase chain reaction (PCR) on a human cDNA sample using a primer that consists of the nucleotide sequence set forth in SEQ ID NO:41 and a primer that consists of the nucleotide sequence set forth in SEQ ID NO:42. Claims 46-56 are drawn to vectors comprising the polynucleotide of claim 45, recombinant host cell containing said vector and isolated membrane of said recombinant cell. Instant fact pattern closely resembles that in Ex parte Maizel, 27 USPQ2d 1662 (BPAI 1992). In Ex parte Maizel, the claimed invention was directed to compounds which were defined in terms of function rather than sequence (i.e., "biologically functional equivalents"). The disclosed compound in both the instant case and in Ex parte Maizel was the full length, naturally occurring protein. The disclosed compound in instant application is a primer SEQ ID NO:41 (27 nucleotides) and SEQ ID

NO:41 (25 nucleotides) which do not even encode the full-length polypeptide. The critical feature of the invention as it relates structure to function is not contained in the primer sequence. In Ex parte Maizel the Board found that there was no reasonable correlation between the scope of exclusive right desired by Appellant and the scope of enablement set forth in the patent application. Even though Appellant in Ex parte Maizel urged that the biologically functional equivalents would consist of proteins having amino acid substitutions wherein the substituted amino acids have similar hydrophobicity and charge characteristics such that the substitutions are "conservative" and do not modify the basic functional equivalents of the protein, the Board found that the specification did not support such a definition, and that the claims encompassed an unduly broad number of compounds. Such is the instant situation. Clearly, a single disclosed sequence does not support claims to any nucleic acid isolated by the process of claims 44, 45 and 58, given the lack of guidance regarding what sequences would hybridize specifically to sequence complementary to the polynucleotide of SEQ ID NO:41 and 42 and not other, related sequences. Further, many of the polypeptides encoded by the nucleic acids isolated will be unrelated to the protein of SEQ ID NO:16, being devoid of its characteristic structural and functional features. The claims encompass variants comprising the primers SEQ ID NO:41 and 42 encoding variants with or without the ability to increase IP3 levels. The limitation "increases an intracellular level of IP3" is a meaningless limitation because when hRUP35 is present in the thalamus it maintains a baseline level of IP3. The term "increases an intracellular level of IP3" only has meaning when compared to something. In instant claims there is

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no comparison. The functional limitation encompasses polynucleotides that may encode other GPCRs unrelated functionally and structurally to that disclosed in SEQ ID NO:16.

For example G-protein coupled receptors associated with Go and Gq activation of the enzyme phospholipase C will have an effect on IP3, this includes other orphan receptors. The specification does not disclose how to use the unrelated orphan receptors encompassed by the claimed method. Further, many compounds isolated may be inactive. The specification does not disclose how to use inactive compounds. Inactive compounds may be truncated polynucleotides devoid of function and lacking the critical feature that relates structure to function. The only thing the primers guarantee is that they will hybridize to a specific region of the polynucleotide, what is amplified is unknown based on the fact that applicant has isolated only one polynucleotide of the genus claimed. Further, in claim 44 the hybridization conditions required for the PCR are not specified. The scope of the group of sequences that would meet the limitations of the claim depend upon the precise conditions under which hybridizations were performed including wash conditions. Since the hybridization and wash conditions dictate which nucleic acid sequences remain specifically bound to the claimed polynucleotide the metes and bounds of the claims cannot be determined without the disclosure of said conditions. Due to the large quantity of experimentation necessary to identify the polypeptides with the structural and functional features of instant invention, the lack of direction/guidance presented in the specification regarding the identification, purification, isolation and characterization of said polynucleotides, the

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unpredictability of the effects of mutation on the structure and function of proteins (since mutations of SEQ ID NO:15 and 16 are also encompassed by the claim), and the breadth of the claim which fail to recite meaningful structural and functional limitations, undue experimentation would be required of the skilled artisan to make or use the claimed invention in its full scope.

As is evidence in the discussions *supra*, undue experimentation would be required by the skilled artisan to make and use the instant invention. Further since the claimed hRUP35 has no utility, vector comprising the claimed nucleic acid, cell comprising said vector, composition comprising claimed nucleic acid, membrane isolated from said cell are also rejected under 35 USC 112, 1st paragraph.

Claim Rejection 35 USC 112, 1st paragraph (Written Description)

11. Claims 44-61 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 44-61 are drawn to an isolated polynucleotide, wherein said polynucleotide comprises a nucleic acid sequence encoding an endogenous human G protein-coupled receptor, said nucleic acid sequence being amplifiable by a process comprising performing polymerase chain reaction (PCR) on a human cDNA sample using a primer that consists of the nucleotide sequence set forth in SEQ ID NO:41 and a

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primer that consists of the nucleotide sequence set forth in SEQ ID NO:42. Claims 46-56 are drawn to vectors comprising the polynucleotide of claim 45, recombinant host cell containing said vector and isolated membrane of said recombinant cell.

It must be noted that the skilled artisan cannot envision the detailed chemical structure of the encompassed compounds and, therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. The claims encompasses polynucleotides that are amplifiable by PCR using two small primers (SEQ ID NOs:41 and 42). The only thing the skilled artisan can envision are the two primers. What they will fish out is unknown and highly unpredictable. Does the applicant know what polynucleotides will be isolated, based on the disclosure they do not. Can they envision the detailed chemical structure of the encompassed compounds before isolation, no they cannot. Applicants are trying to claim variants that they do not know even exist. For example the post filing art discloses splice variants of RUP35, applicant had no idea they existed at the time of filing instant application, they are probably encompassed by the claims. There are probably many structural variants present in the thalamus that as structurally unknown to applicant, but are encompassed by the claim.

Claim 44 does not even disclose the conditions required for the PCR reaction. The sequences that would be amplified depend upon the precise conditions under which hybridizations were performed including wash conditions. Claim 44 provides a limited structural limitation and no functional limitation. Claim 45 further limits claim 44 by requiring expression of the polynucleotide in the thalamus and increase in

intracellular level of IP3. Being present in the thalamus is not a functional limitation, it says nothing about the activity of the endogenous GPCR as it relates structure to function. The limitation "increases an intracellular level of IP3" is a meaningless limitation because when hRUP35 is present in the thalamus it maintains a baseline level of IP3. The term "increases an intracellular level of IP3" only has meaning when compared to something. In instant claims there is no comparison. The only thing the primers guarantee is that they will hybridize to a specific region of the polynucleotide, what is amplified is unknown based on the fact that applicant has only isolated only one polynucleotide of the genus claimed. The primers will bind to a DNA in a sample. The structure of what will be isolated is unknown. Whether the isolated structure will contain the critical feature of the invention as it relates structure to function is unknown. Applicant has disclosed one polynucleotide, SEQ ID NO:15. Based on approximately two pieces of polynucleotide approximately 50 nucleotides which do not even contain the critical feature of the invention as it relates structure to function, applicant is claiming stretches of unknown polynucleotide which may be much greater than 1000 nucleotides in length. Applicant has not isolated or made anyone of the sequences encompassed by the claims, except the single polynucleotide of SEQ ID NO:15. In essence Applicant wants to go on a fishing expedition and keep any molecule that even closely resembles a GPCR, whether it has the structural features that give it the functional limitation of SEQ ID NO:15 or not. These claims essentially are a license to fish and keep anything that gets snagged on the hook. Based on the primer sequence there is no way to predict what the structure of the isolated sequence between the two primers will be.

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There has been no reduction to practice of any polynucleotide claimed except that disclosed by SEQ ID NO:15.

The ability to hybridize to the primers does not disclose the critical feature of the invention that is required for activity for hRUP35. Therefore nucleic acid molecules encoding variants of the protein disclosed in SEQ ID NO:16, said variants may be completely unrelated, structurally and functionally to the protein encoded by SEQ ID NO:16 are encompassed by the claims. The common function of the nucleic acid (SEQ ID NO:15) encoding the polypeptide (SEQ ID NO:16), which is based upon a common property or critical technical feature of the genus claimed is not disclosed. The ligand that binds hRUP35 is not disclosed. The claims, as written, encompass nucleic acid encoding polypeptides which vary substantially in length and also in amino acid composition. The instant disclosure of a polynucleotide of SEQ ID NO:15 encoding the polypeptide of SEQ ID NO:16 does not adequately describe the scope of the use of the claimed genus, which encompasses a substantial variety of subgenera including polynucleotides, variants of said polynucleotides, allelic variants, chimeric constructs, fusion constructs which may encode polypeptides completely, unrelated functionally to the polypeptide of SEQ ID NO:16. A description of a genus of polypeptides may be achieved by means of a recitation of a representative number of polypeptides, defined by amino acid sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Instant specification fails

to provide sufficient descriptive information, such as definitive structural and functional features of the claimed genus of polypeptides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. For example, what regions and fragments of the claimed hRUP35 contain a definitive structural feature required for protein function? The specification proposes to discover other members of the genus by using screening assays and techniques involving probes, primers, and hybridization. There is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides and proteins encompassed. No identifying characteristic or property of the instant polypeptides/polynucleotide is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of specific polypeptide and nucleotide sequences and the inability to screen, is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe, enable and use the genus as broadly claimed. The skilled artisan cannot envision the detailed chemical structure of the encompassed proteins and, therefore, conception is not achieved until reduction to

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practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. It is acknowledged that the skill of the artisan in the molecular biology art is high. However, in the current instance, there is no clear evidence of the specific activity possessed by the claimed genus of nucleic acid molecules encoding variant hRUP35 polypeptides, the critical special technical feature of the polypeptides or how the critical special technical feature encompassed by the genus claimed relates to function. Because of the lack of guidance in the prior art and current application, one skilled in the art could not predict if the variants hRUP35 have the same activity as the protein disclosed in SEQ ID NO:16, since no activity is disclosed, or if they contain the domain(s) of SEQ ID NO:16, containing the critical special technical feature of the claimed hRUP35, since no critical special technical feature is disclosed. The specification discloses hRUP35 is an orphan receptor, i.e. Receptor with no known ligand and function

The skilled artisan cannot envision the detailed chemical structure of the encompassed compounds and, therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written

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description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115). Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid or polypeptide is itself is required. See *Fibers v. Revel*, 25 USPQ d. 1601 at 1606 (CAFC 1993) and *Amen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Furthermore, In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". Therefore the specification fails to disclose the activity of the claimed genus of polypeptides/polynucleotides, the critical special technical feature of the polypeptides/polynucleotides or how the critical special

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technical feature encompassed by the fragments and variants of claimed hRUP35 relates to function.

The claims encompass nucleic acids encoding proteins which are structurally and functionally unrelated to the protein/nucleic acid disclosed in SEQ ID NO:16 and 15, respectively. Therefore instant specification fails to provide sufficient descriptive information, such as definitive structural/ functional features of the claimed genus of nucleic acids/polypeptides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no disclosure of the specific activity of claimed hRUP35 and how it is specifically assayed. Neither specification nor claims disclose the specific activity of the HRUP35 of instant invention or a description of the conserved regions which are critical to the structure and function of the genus claimed.

The claimed nucleic acid encodes an orphan receptor hRUP35 whose activity, associated function and activating ligands have not been disclosed. The neither specification nor prior art provide a specific assay for the genus claimed. The superfamily of GPCRs is specialized proteins designed for chemical recognition of specific ligands and subsequent transduction of information encoded in those ligands/compounds to the machinery of the cell. GPCRs interact with many diverse compounds having diverse effects. The important features which would help to define the hRUP35 activity and define the genus claimed have not been disclosed in the specification nor prior art. Further the activity transduced is not disclosed or how it relates structure to function.

Therefore instant specification fails to provide sufficient descriptive information, such as definitive structural/ functional features of the claimed genus of polypeptides/polynucleotides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no disclose the specific activity of the orphan hRUP35 of instant invention, nor any description of the conserved regions which are critical to the structure and function of the genus claimed. Further vector comprising the claimed nucleic acid, cell comprising said vector, composition comprising claimed nucleic acid are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim Rejection, 35 U.S.C. 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 41, 43, 44-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "increases" in claims 41, 43, 45 and 61 is a relative term which renders the claim indefinite. The term "increases" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary

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skill in the art would not be reasonably apprised of the scope of the invention. The claimed polynucleotide encodes an endogenous polypeptide (hRUP35) which when present in the cell provides a baseline level of IP3. It is not clear what the increase in an intracellular level of IP3 is in relationship to? The IP3 levels in the cell will increase or decrease in relationship to a baseline when hRUP35 in the cell is stimulated or inhibited. It is not clear, without the stimulation of hRUP35 with an agonist how the intracellular level of IP3 will increase?

Claim 44 is indefinite because hybridization conditions required for the PCR are not specified. The metes and bounds of the group of sequences that would meet the limitations of the claim depend upon the precise conditions under which hybridizations were performed including wash conditions. Since the hybridization and wash conditions dictate which nucleic acid sequences remain specifically bound to the claimed polynucleotide the metes and bounds of the claims cannot be determined without the disclosure of said conditions.

Claims 46-60 are indefinite because they depend on an indefinite base claim and fail to resolve the issues raised above.

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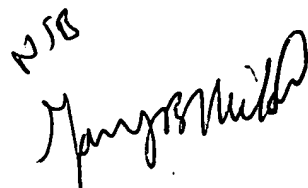
Advisory

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal S. Basi whose telephone number is 571-272-0868. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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8/30/06



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